Interstitial Lung Disease: Altering the Course Through Effective and Individualized Management

Steven Nathan, MD and Imre Noth, MD

Overview: Steven Nathan, MD, and Imre Noth, MD, provide their insights into the challenging management of patients with an interstitial lung disease. They stress the importance of the differential diagnosis of ILD and the role of the multidisciplinary team in establishing the diagnosis as both have important treatment implications. Following a review of treatment principles, Drs. Nathan and Noth provide extensive discussion of treatment options, including antifibrotic medications, lung transplantation, pulmonary rehabilitation, and other options. They delve into the difficulties encountered in treating acute exacerbations and the importance of initiating palliative care early in the disease course. With an eye to the near future, they conclude with the evolving role of genetics in delivering personalized medicine.

Content Areas

- Definition and epidemiology
- Pathogenesis
- Evaluation and diagnosis
- Nonpharmacologic and pharmacologic treatment
- Acute exacerbations
- Palliative care
- Future directions

Target Audience

This activity was developed for pulmonologists, rheumatologists, and other clinicians who may encounter patients with interstitial lung diseases and/or connective tissue diseases.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Diagnose interstitial lung diseases in a timely manner through optimal use of diagnostic criteria and radiologic findings
- Chart disease course during the management of ILDs
- Optimize treatment response in the management of ILDs with appropriate assessment and follow-up
- Develop evidence-based, individualized treatment plans for ILD management

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Steven Nathan, MD
Professor of Medicine
Virginia Commonwealth University
Director, Advanced Lung Disease and Lung Transplant
Inova Fairfax Hospital

Imre Noth, MD
Professor of Medicine
Chief, Division of Pulmonary and Critical Care
University of Virginia

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ALTERING THE DISEASE COURSE THROUGH EFFECTIVE AND INDIVIDUALIZED MANAGEMENT

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Editor's Note

This is a transcript of Dr. Steven D. Nathan's and Dr. Imre Noth's presentation "Interstitial Lung Disease: Altering the Disease Course Through Effective and Individualized Management."

Introduction

Steven Nathan, MD: Interstitial lung disease encompasses a large number of heterogeneous conditions that are characterized by variable amounts of inflammation and/or fibrosis. You can have some of these conditions that are mostly inflammation, others that are fibrosis. Even though there are 150 plus different courses, many of these interstitial lung diseases share common CT findings, physiologic changes, pathologic manifestations, and each of them can have a variable course. Some of them have a rather poor prognosis. Other ones can be entirely reversible. There's a wide spectrum of these different diseases in terms of the manifestations and potential outcomes. Some of them can carry a significant morbidity as well as mortality, and for most of them there's little consensus on the best forms of management.

What is interstitial lung disease? It's variable diseases that involve the interstitium of the lung. They don't necessarily involve all the other aspects, although there can be some involvement of all the other air spaces, but that fine lattice work that constitutes the interstitium of the lung is the primary area where the disease manifests. Typically you can see this on chest x-ray. You can see it more in greater detail on a chest CT and it involves both lungs diffusely. Sometimes upper lobes might be more involved, sometimes the lower lobes, but invariably it is a form of diffuse parenchymal lung disease.

Here we have a demonstration pathologically of what normal alveola look like, and to the right we have changes that might be seen with various forms of interstitial lung disease where there's diffuse fibrotic changes present through the lung.

How do we categorize interstitial lung disease, variably known as diffuse parenchymal lung disease? On this slide you can see one of the categorizations, which is a little complex in terms of known cause or association, things like connective tissue disorders, occupational diseases. We have the broad group of idiopathic interstitial pneumonias. We have the granulomatous diseases, and then we have other unique entities that are typically more rare, such as pulmonary alveolar proteinosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell granulomatosis, all quite a mouthful.
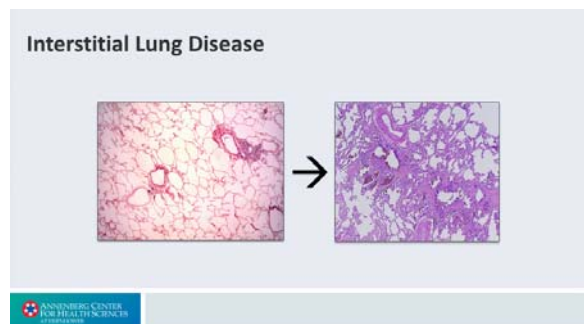
Perhaps a more pragmatic, easier way to categorize these diseases—the pneumonic is quite easy. There's 5 I's, a C, and an N. If you think about these 6 or 7 broad categories, you'll cover all the different diseases that can give you interstitial lung disease. Under the idiopathics
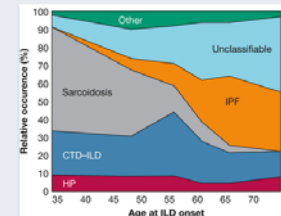
we have the IIPs, or idiopathic interstitial pneumonias, and we have our alphabet soup, shown on the right, of the different disorders, the most common being idiopathic pulmonary fibrosis. Then, we have nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), respiratory bronchiolitis interstitial lung disease (RB-ILD), etc. Other idiopathic entities include sarcoidosis, amyloidosis, and some of the other rare entities that I mentioned previously.

Under the next "I," which are immunologic, because we have the various connective tissue disorders. The third "I" is the inhalational disorders, things like hypersensitivity pneumonitis and then inorganic materials that might be inhaled, resulting in conditions like asbestosis or silicosis. The iatrogenic, what we do to patients with some of our interventions, including antiarrythmics drugs, antimicrobials, chemotherapeutic agents, and radiation therapy. The fifth "I" are infections. This is usually quite evident clinically. Patients will present with infectious symptoms, but certainly viral infections, fungal infections, can give you diffuse parenchymal changes that might mimic interstitial lung disease. Chronic congestive heart failure if left untreated for many years, we don't see that much these days, but that can give you diffuse interstitial changes as well. Then, various neoplastic conditions like lymphangitic carcinomatosis can give you diffuse interstitial lung disease, too. Remember 5 I's, a C, and an N, and you won't forget much.

Interstitial lung disease is an umbrella term encompassing all these different conditions, whereas IPF is a very specific form of interstitial lung disease. IPF is one of the diseases, the prototypical disease categorized under the idiopathic interstitial pneumonias. When we talk about pulmonary fibrosis, we talk about any lung condition that can result in fibrosis. This can get somewhat confusing in terms of the nomenclature. IPF can give you fibrosis, sarcoidosis can give you fibrosis, and pulmonary fibrosis does not refer to specific disease entity.

A study that came out fairly recently looking at the distribution of interstitial lung disease by age of onset. This study included over 300 patients and you can see in the diagram by age, the relative prevalence of these different disease conditions. You'll note that as patients age, the likelihood of this being IPF gets higher. IPF is a disease of the elderly. You can also see from this particular study that the number of patients with unclassifiable disease also increases as they get older. Now, practice habits differ in different institutions and my bent and bias is if a patient is more elderly in the context of unclassifiable, there's a good chance that these patients have IPF, because it is a disease of the elderly. Some of these unclassifiable in this particular study might indeed have had IPF.

What about interstitial lung disease complicating the various connective tissue disorders? This can be a source of significant morbidity and mortality. The estimates of the

number of deaths in the US from CTD-ILD is about 1600 annually. This might be more. This data's a little bit dated. About 25% of all ILD deaths are attributable to an underlying connective tissue disease. In terms of the relative prevalence amongst the different diseases, rheumatoid arthritis, estimated 15% to 20%, polymyositis and dermatomyositis, around the same range, 5% to 20%, SLE, lupus a little bit less, 5% to 18%, scleroderma very common, 50% to 70%, and lastly Sjogren's, around 5% to 40%. So a wide range in terms of how these diseases might be complicated by underlying CTD, the underlying ILD, rather.

Let's talk about rheumatoid arthritis. First, it can be the presenting manifestation in up to 15% to 20% of cases. Cigarette smoking is a risk factor. It's the most common pulmonary complication within the first 5 years. If it's going to complicate a patient with rheumatoid arthritis it's usually seen within the first 5 years. Pulmonary complications account for about 10% to 20% of mortality seen in rheumatoid arthritis. The incidence, or prevalence rather, of subclinical lung disease is significantly higher than in those patients who manifest with pulmonary symptoms. Once again, perhaps not mentioned previously, it tends to be more common in males who have rheumatoid arthritis than females.

Moving on to scleroderma, the prevalence is quite high. It is a very common manifestation of the disease, and as opposed to rheumatoid arthritis, if one looks at the pathological pattern that we see in scleroderma, it's usually a nonspecific interstitial pneumonia (NSIP) type of pattern in most cases. Rheumatoid arthritis, most of the cases tend to be usual interstitial pneumonia (UIP). For all the rest of the connective tissue diseases, it's mostly NSIP pattern, although UIP can be seen as well.

Sjogren's Disease is a little bit different since the most common pathologic picture here is lymphocytic interstitial pneumonia. Interstitial lung disease can be seen in about 5% to 40% of the cases. Other pathologic entities that might be seen include chronic bronchiolitis, organizing pneumonia, NSIP, UIP. Some of the cases can even go on to develop lymphoma of the lung.

Let's move on to idiopathic pulmonary fibrosis. This is defined or characterized as a chronic and progressive disorder that may be fatal. It's characterized by progressive scar formation, with no apparent etiology or precipitating factor. It tends to have a characteristic pattern on high resolution CT of the chest. Although, you can have IPF with somewhat atypical appearing CT patterns, but the CT is the pivotal study that determines the diagnostic algorithm for these patients, and in the appropriate clinical context. If you have a UIP pattern, this might be enough to make the diagnosis. An important point though is if you have an inconsistent UIP pattern, some of those patients, especially elderly patients, might still turn out to have IPF. Now, we talk about this term UIP, it was initially a pathologic description usual interstitial pneumonia. This crept its way into the radiographic lexicon nomenclature where we talk about a CT UIP pattern and then you also have a pathologic UIP pattern.

Clinically, patients with IPF present with shortness of breath, typically over the course of many months and sometimes this is associated with a hacking, dry cough. In some cases, it may be 10% to 15% of cases, patients present with cough alone before the onset of shortness of breath. If you think about IPF and how common it is, it's not very common in relation to other more common causes of shortness of breath. A lot of times patients will go misdiagnosed. They might be diagnosed as asthma, COPD, heart failure very common in the elderly as well. It is very important to be aware of this condition and to be on the lookout for things that distinguish IPF from these other more common entities that might present with the same features. One of the typical findings on chest exam that might alert a clinician to the presence of IPF are the distinctive inspiratory Velcro crackles that are typically heard at the

bases. IPF is a disease that carries with it significant potential mortality with the median survival estimated at anywhere from around 3 to 5 years.
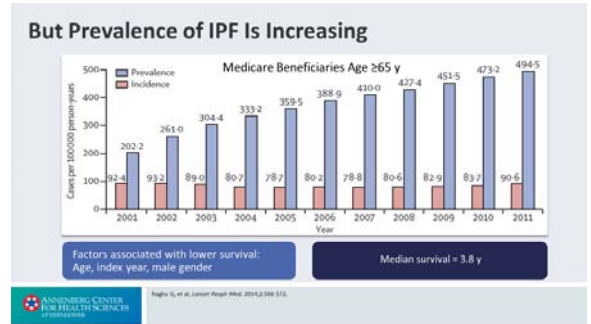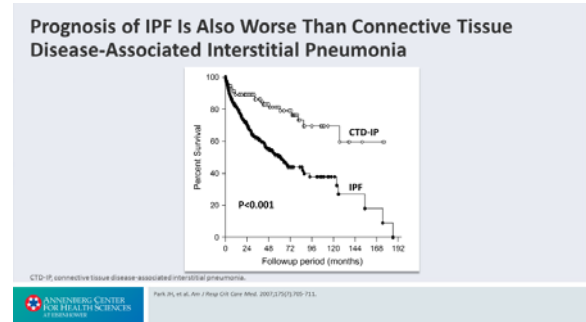
As mentioned previously, and as depicted in this slide, IPF is a disease of the elderly. The older the patient, the more likely it is that whatever ails him in terms of interstitial lung disease is going to turn out to be IPF, even though it is a relatively rare condition that accounts for about one-third of all lung transplants that are performed nationwide.


The prevalence of IPF is actually increasing. The study was taken from a large, Medicare database and this alerts us to the fact that we are seeing more and we'll continue to see more IPF in the future. The prognosis trends to be quite poor.

From this particular study, the number of patients surviving to 5 years was around under 40%. If you look at this in the context of cancers, IPF has a worse prognosis than most or many different forms of cancer. The only cancers that have worse prognosis than IPF are stage III and stage IV lung cancer, and pancreatic cancer.
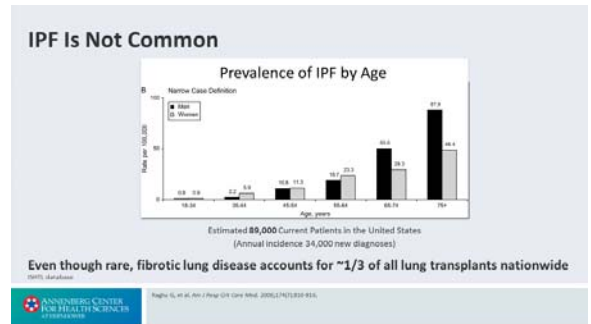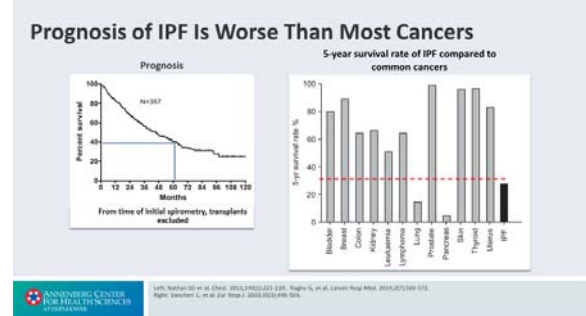
It is important to make the distinction of IPF vs other forms of interstitial lung disease because what we tell patients in terms of prognosis is quite different. For example, IPF has a significantly worse prognosis than patients with an underlying connective tissue disease. Hence, the reason to make an accurate diagnosis, because it has prognostic implications and as you'll hear, also has treatment implications as well.

Something that is getting more attention is an entity that's been termed interstitial lung abnormalities or rather early interstitial lung abnormalities. There was a paper that was published that looked at 4, large databases, or cohorts, of patients who enrolled in various clinical trials. There was a Framingham Heart Study, the AGES study, which was an Icelandic study, the COPD Gene study, and the ECLIPSE

study. A couple of thousand patients in each of these studies, and what was common to all of these studies was that patients had to have a screening baseline CT scan at the start of enrollment. What these authors did was they went back and they looked at the presence of interstitial lung abnormalities on the initial screening CTs, and they followed up on these patients with and without interstitial lung abnormalities to see what the outcomes were.

A very common feature to all of these studies was that those patients who had interstitial lung abnormalities had worse outcomes and a greater likelihood of mortality in the ensuing years. What was also interesting—and quite common through all these 4 studies—was the prevalence of early interstitial lung abnormalities, which was around 7% for all of these cohorts. The message from this was the presence of early interstitial lung abnormalities has clinical meaning, and the reason why some of these patients likely have a higher mortality was that some of them evolved to develop various forms of interstitial lung disease, the most common, most likely being idiopathic pulmonary fibrosis, and that's why, through the years, we see these curves come apart.

Association Between Interstitial Lung Abnormalities and All-Cause Mortality
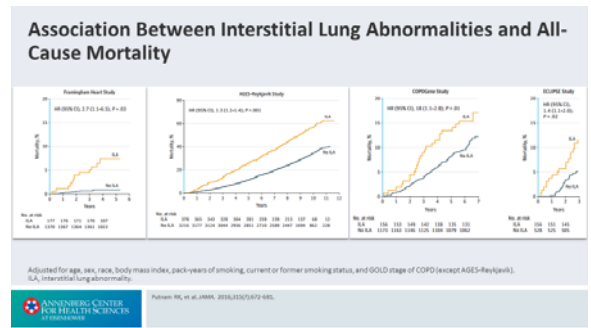
In summary, the interstitial lung diseases are a broad category of different diseases, 150 plus, if you read or open any textbook. It becomes very important to discern all these different conditions from one another, because their prognosis is very different and the management is very different. The prototypical disease of the idiopathic interstitial pneumonias is IPF. That constitutes about two-thirds to three-quarters of all their idiopathic interstitial pneumonias. With the availability now of antifibrotic therapy, it's become increasingly important to make the diagnosis early and to differentiate IPF from all the various other forms of interstitial lung disease. Thank you for your attention.

Pathogenesis

Imre Noth, MD: In this module, we will discuss our current understanding of the highly complex pathogenesis of interstitial lung disease by discussing what we know about interstitial pulmonary fibrosis.

On this first presentation what we see is the fibroblast and epithelium interacting with lung injury leading to some kind of process. And we are expecting to see a certain amount of cell death or reprogramming at the capillary and epithelial level.
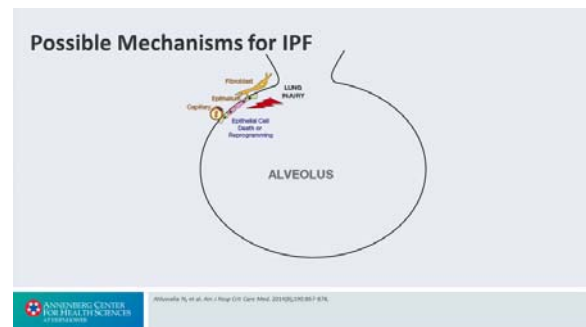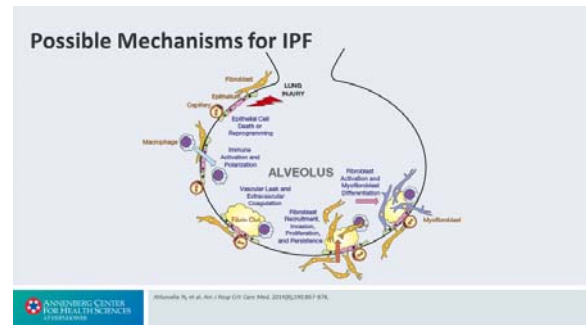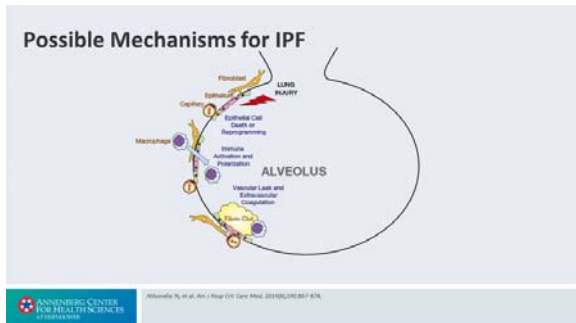

As we move to the next stage, the results of that lung injury lead to an inflammatory process. And that inflammatory process is immune-mediated with immune activation and polarization of macrophages that get drawn into the alveolar space.
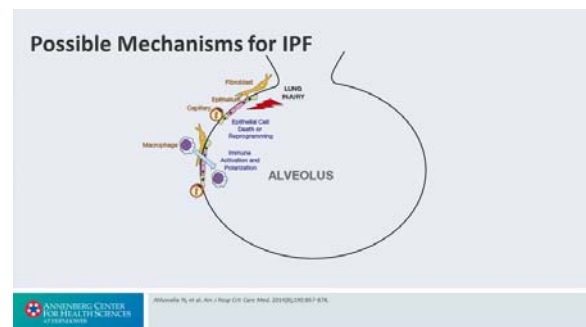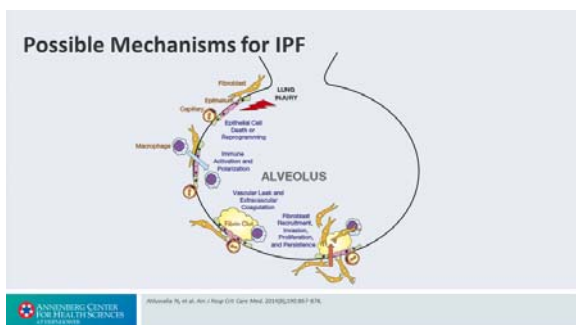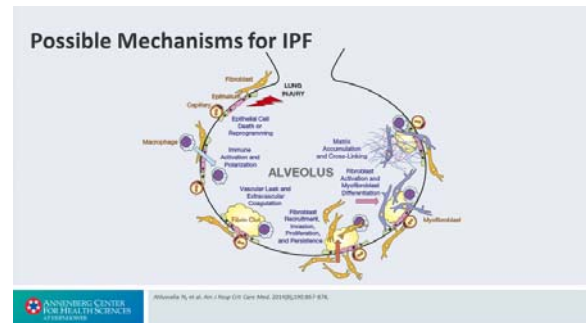
Those macrophages then provide the cytokines and interleukins, if you will, that lead to a vascular leak and extravascular coagulation. And finally a fibrinous clot, which is meant to seal off the area of injury in a normal process.

We then see that there is a recruitment of various cell lines to help that repair process including fibroblast recruitment and invasion and proliferation and persistence of those cells. In fact, one of the major thoughts in regard to pulmonary fibrosis is that the fibroblast cell line becomes immortalized while the epithelial cells unfortunately die.

The next build on that is activation of those fibroblasts and differentiation into a myofibroblast, which is a more universal cell with greater pleiotropic activity, that helps maleate that process. The fibroblasts, in differentiating to that process, create worlds of cells called fibroblastic foci, which seem to drive the fibrosis forward.
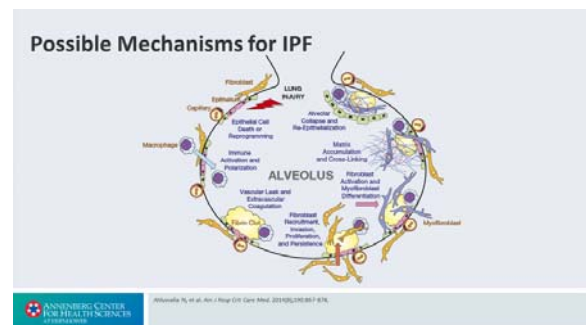

They then lay down the extracellular matrix which is really the fibrotic component or the building blocks involved in that fibrotic component. And that matrix leads to crosslinking and accumulation, creating that fibrosis.

Finally, we see the alveolar collapse and re-epithelization of that region. As it gets sticky, if you will, and the fibrosis shrinks down like any scar that you would have on the back of your hand, it causes restriction and a stiffness in the lung. This is just one of the outlying possible mechanisms that's been proposed to help put the context of the disease into place.
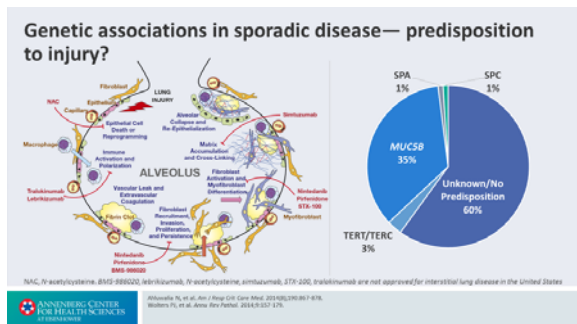
[In] the last portion of the build slide, what we see is an integration of really 2 parts. The first is showing some of the mechanisms involved and their interaction with various interventions. Those might include things like N-acetylcysteine, lebrikizumab, nintedanib, and pirfenidone, and other monoclonal antibodies acting at the various portions. What that's showing you is that the particular agents in development are really starting to focus in a far more targeted fashion at where the mechanisms of action may be occurring. Directed monoconal activity at the immune activation, less directed activity involving nintedanib and pirfenidone at fibroblast recruitment and certainly at fibroblast activation. And then finally directed monoclonal activity at the accumulation and cross-linking of the alveolar matrix.

The last part is really integrating the underlying genetics. We know that there's a clear predilection in these patients involving certain predispositions of common polymorphisms and uncommon polymorphisms. A largest group being the MUC5B polymorphism, which represents about 35% of the patients. Now this is not an abnormal polymorphism. It's very important to recognize that. It exists in 10% of the populous and 35% of the patients. So 10% of the populous is certainly not abnormal, it's just a minority of them. We know that by risk-stratifying for these things, that we can try to begin to understand where the effects may be in this hypothesis over the possible mechanisms involved in initiating alveolar fibrosis.

In summary, we have many possible mechanisms of action with a cascade that's been demonstrated to you by that last figure. The first is really the integration of the injury with the repair process, the accumulation of the immune activation system. The fibroblast being mediated into myofibroblasts and immortalization, if you will, with proliferation. And the loss of the epithelial integrity. What that does, though, is provide a framework for where individualized therapies may be developed and directed at each step. And hopefully provide a cascade of steps that can then be used in concert to have a greater impact on the disease. Then finally how the genetics may play some role in mediating that process.

Evaluation and Diagnosis

Imre Noth, MD: In this module, we will discuss the evaluation and diagnosis of interstitial lung disease.

First you notice that subway map and I'm going to show you here how this confusion kind of continues, but I want it in a more conceptual fashion. So this diagnostic algorithm for ILD helps marry the key things that we always engage in, in any approach in medicine.
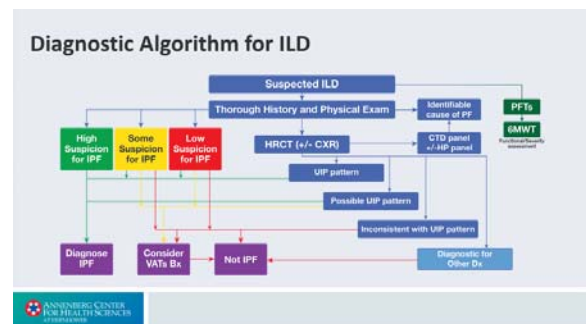

The first is really our clinical suspicion for whatever the underlying disease process is and the second is the integration of the objective data. What this slide has done is shown you that process. So when we have a patient with a suspected ILD, our first role is really just a history and physical. We ask ourselves, "Is there

a high suspicion for IPF, some suspicion, or low suspicion?" The most powerful tool that we have is the high-resolution CT scan. I'll talk a little bit more about that. But the first part is identifying if there are other causes, and then integrating that into the data, and then integrating the possible patterns that we see on that CT scan to make a diagnosis.
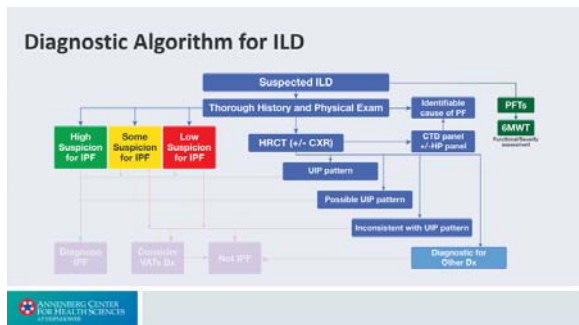
Now you see that there's an integration of the green line, if you will, which incorporates the clinical suspicion with the CT data to help build out a possible diagnosis. If the CT scan is consistent with the usual interstitial pneumonia pattern, you'll notice that with a high suspicion, we move directly towards diagnosis of IPF. Whereas, if there's only some suspicion, or only a possible UIP pattern, we move into considering a biopsy by video-assisted thoracoscopic approach.
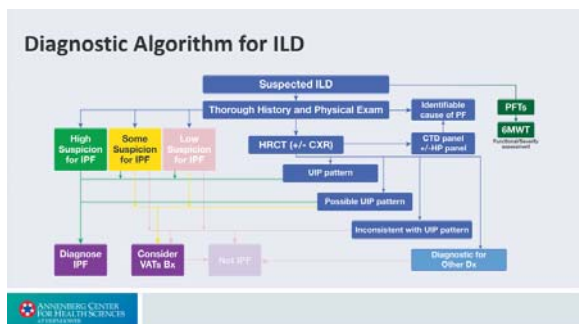
Then on the red line, if it's an inconsistent pattern of the CT scan, this is where we're going to consider alternative diagnoses.
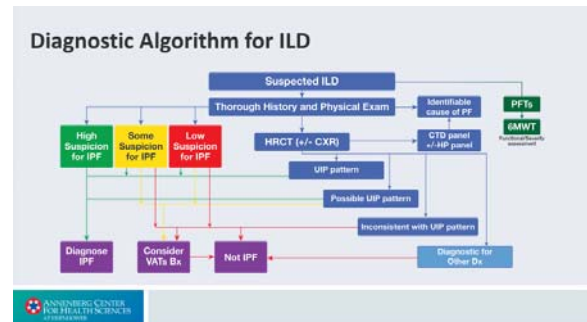
As we look at the approach from a pulmonologist's standpoint for the workup, we ask 3 questions. Is there a discernible cause for the ILD, and if not, does it appear to be idiopathic pulmonary fibrosis? And then finally, if neither of the above, should a biopsy be done to further decipher the underlying process?

What's involved in the workup? Well, the first thing that we ask is, has this been around for a long time or is this acute? Is this acute or chronic? Are there possible exposures? This might involve the underlying job of the person, hobbies, things like, it might sound very eclectic, but glassblowers.

I spent 22 years in Chicago, and silicosis and asbestosis were very high on the list because of the steel mills. Certainly, mold from hot tubs or moldy basements. We ask ourselves about comorbidities and you'll see, as we move forward, why this becomes so important. But it does become a question of pattern recognition because we know that there's a higher predilection to certain comorbidities with this diagnosis and the alternative diagnoses as well.

Then we look for the evidence of autoimmune diseases. Things like mechanic's hands or sclerodactyly or arthritis. We are certainly going to look at the spirometry and the diffusion capacity. This helps us discern the level of restriction and whether it's present or not.

Laboratory work, this is highly important in discerning whether or not an autoimmune

disease is present. Now it's true that some of the lab work, such as an antinuclear antibody (ANA) and an erythrocyte sedimentation rate (ESR), may be elevated in the elderly. But the other ones become very, very specific and very important to certain disease processes. Things like an SCL-70, which will be highly indicative of an underlying scleroderma process, or an SS-A or an SS-B, which would suggest Sjogren's. Alternatively, something like an antisynthetase testing with an anti-Jo would suggest polymyositis.

Most importantly is the high-resolution CT scan because it helps us get at the pathology without needing a biopsy. We know that if there is a usual interstitial pneumonia pattern on the CT scan, it's almost certainly going to be there on the biopsy as well. What we are really trying to discern is whether or not something else may be present, such as a nonspecific interstitial pneumonia pattern or a hypersensitivity pneumonitis pattern.

When we look at the CT scan, we get more information than just the biopsy possibilities. Our radiology colleagues are very good at helping us. So, some of the first questions are really corollaries to the underlying pathology. Is it reticular or is it nodular? If it's reticular, it's going to suggest an interstitial process, if it's nodular, it's going to suggest a granulomatous process. If its interstitial, is there ground glass? Ground glass would represent an alveolitis.

Where is it predominant? Upper vs lower, peripheral vs central. You see upper lobe predominance would suggest things like silicosis. A peripheral process would suggest something more like the usual interstitial pneumonia pattern, whereas the central would exclude it. The truth is that, as I said, our radiology colleagues would be able to make a definitive diagnosis here 60% to 80% of the time, depending on the underlying pattern.

What's the utility of a lung biopsy? This is going to vary greatly depending on what you think it is. We know that a transbronchial biopsy in the setting of something that's granulomatous could be very high. An example would be sarcoidosis, where we know that 90% to 96% will be attainable by transbronchial biopsy. But for something that's not going to be granulomatous, the transbronchial biopsy may have very low yields, under 38%. And certainly a video-assisted thoracoscopic biopsy, or an open lung biopsy, is not always required. But when it is, we want to get 2 sources. And that's to get confirmatory biopsies so that we're not biased by acquisition. Areas of honeycombing should be avoided because those are always going to represent end-stage lung disease.

Now the bronchoalveolar lavage fluid may be useful in certain instances, primarily infectious etiologies. But other things like pulmonary alveolar prognosis, certainly things like a suspected malignancy or drug-induced lesions, such as pulmonary interstitial eosinophilic syndromes, where you might see a rise in the underlying eosinophil counts.

Now is a challenging time, with more IPF, more than ever to really make the right diagnosis. And this is because making the right diagnosis has become not only a constant challenge, but has more impact now than it ever has.

[T]here is a great study out of Columbia a few years ago [that] demonstrates the sooner patients are referred to a specialized center the better they do. And that's independent of how severely they are sick. That's really important, and I think it reflects a few key details. It isn't that referral centers are smarter, it's that usually they have a greater resource allocation to these specific and uncommon diseases. It's simply the Henry Ford principle of patient care. The more you do things over and over again, with an algorithm, the greater the likelihood you are going to make an impact in these patients' lives. And so often these patients see multiple doctors before getting the correct diagnosis and that's really a reflection of the uncommon nature of these diseases with a

really common set of symptoms leading doctors to look at other things first—that's normal. But it's important that we raise the awareness and get them to specialized centers sooner rather than later.


When we consider the diagnostic algorithm for IPF, this is a much more simplified version of that subway set of lines that we were showing. We have a patient with a suspected diagnosis of IPF, we look for identifiable causes for an ILD, if there is one, we immediately move to the right where the diagnosis is not IPF. But if not, we look at the high-resolution CT scan, if it's a classic UIP pattern and there's not another identifiable cause, that's a UIP patient with an IPF diagnosis.
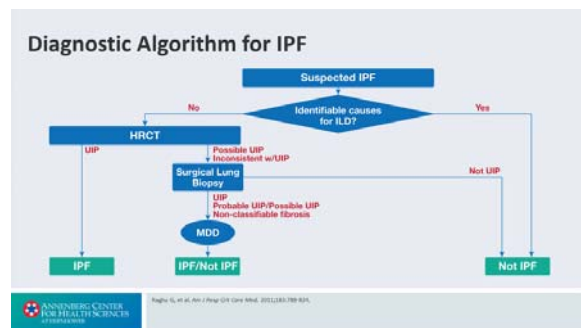
Only the patient in between might need a surgical lung biopsy and the key part here is that circle showing the MDD or the multidisciplinary discussion that really should be had at that juncture in this cadre of patients, probably representing about 15% of the

patients, to determine whether or not they have IPF.

What's that usual interstitial pneumonia pattern? Here we have the CT scans demonstrating that what we can see the honeycomb pattern on the edge or the outside of the lung. These are holes, cystic holes that are seen when they are present, there's a greater than 95% chance that if you biopsy this patient the surgical biopsy will show a usual interstitial pneumonia pattern.

Now that term is important. All that means is the usual or most common type of scar. When you look at this slide it really says everything we need to see. At first, what you notice is the juxtaposition of the normal lung and on the left side of the slide vs abnormal fibrotic tissue on the right.

In the center, when we do the build on the slide, you see what is called the fibroblastic foci. These are the fiberglass lined in parallel leading, they are the leading edge of the extracellular

matrix. This is where the scar tissue gets deposited.

Usual Interstitial Pneumonia (cont)
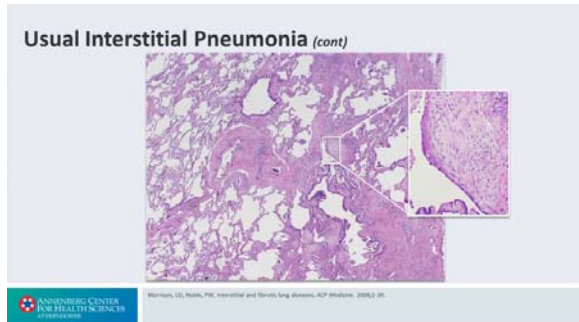
What's also important to recognize is the term simply means the most common type of scar, it does not mean IPF. For it to be IPF, it has to be without an etiology. You can certainly have this pathology with an etiology. And we have the 2 examples here of the UIP pattern in panel A vs this far more blue pattern, if you will, in the slide B portion, and that really represents the greater increase in cellular inflammation. It's far too blue to be IPF.

UIP ≠ IPF

A — IPF
B — Too blue!

How do patients with IPF often present? The most common presentation is shortness of breath and usually on exertion. They often present with dry cough, with some measure of fatigue, with exertional dyspnea, so exercise de-saturation. This is a key point: if you have abnormal normal lungs with scarring, you are going to drop your oxygen level when you exercise. When you have normal lungs, your oxygen level actually goes up. The Velcro rales or crackles at the lung base are going to be present there almost universally. And the clubbing on the fingers and toes may be present in 50% to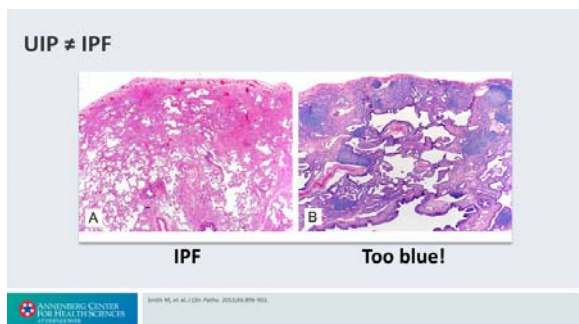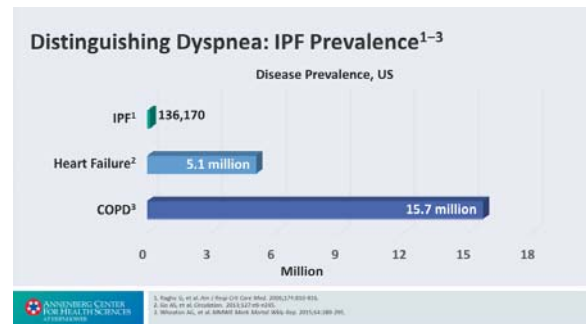 75%. It's often discovered incidentally, usually on a routine chest x-ray or CT scan, and as I mentioned on the previous CT scans that I showed you, we really see it at the bases. It's been noted down on fluoroscopy for cardiac catheterization. And will really be discovered often while taking a family history as well.

All right, let's talk a little bit about dyspnea or shortness of breath.

It is important to recognize that the patient is really going to come in complaining of that, and this is why it takes so much time to work them up. We know that there are roughly 16 million Americans with COPD who are going to have some presentation of shortness of breath. Heart failure 5.1 million Americans, whereas IPF is only going to be represented by the 136,000 cases. Now, what's one of the things I like to teach the medical students about, the number one cause of dyspnea worldwide? [It's] anemia, and it's going to dwarf all of these.

Distinguishing Dyspnea: IPF Prevalence[1–3]

Disease Prevalence, US

IPF[1]	136,170
Heart Failure[2]	5.1 million
COPD[3]	15.7 million

Context is important, where you are, who you are, and what the other common risk factors look like. So, when we think about that, we quickly realize that this is a disease of the elderly—it's 3 times more common in an 80-year-old than a 50-year-old. It's a male predominant disease; 4:1 more in men than in women. We know there's a high predilection towards smoking. We know there are higher rates of reflux disease, 60% to 80-% will have some measure of reflux.
We know that they have often had exposures of some kind, even though those may not have been an etiology. So exposures to metal dust or

wood dust, and as we mentioned in a previous module, our genetic predisposition.

What do those comorbidities look like and what are their impact? This is a great study out of the German natural history cohort that looked at 272 patients in the tertiary care database, and comorbidities mattered. Not only were they implicative of the disease, but they also implied differences in survival. So here we have a long list of multiple comorbidities associated with interstitial pulmonary fibrosis at higher rates. Things like coronary disease, which is 4 times more likely. Lung cancer rates, reflux disease, depression, anxiety, venous thromboembolic disease. You will notice the asterisked ones. You are more likely to die when you have these elements. Coronary disease—highly implicative of an increase in death. Lung cancer certainly more so. And even reflux disease seems to have some impact. We know that the median survival is decreased from 66 months to 12 months with 6 reported comorbidities.
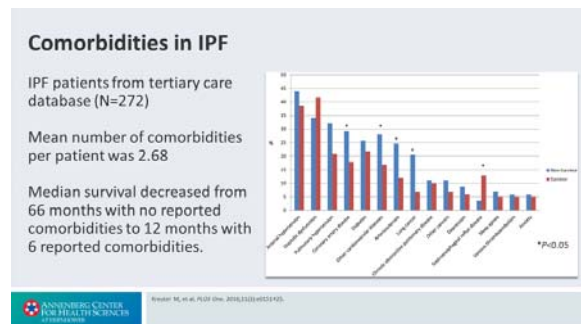
What are other elements that predict outcomes in these patients? We know if you desaturate when you walk below 88%, that is a very bad prognostic sign. This is now data that is a decade and a half old, by Lama at the University of Michigan where they simply took a look at a small cohort of patients to demonstrate if they desaturated, that was bad. It shouldn't be a surprise. Reflecting the fact on that, patients who desaturate often have worse pulmonary hypertension, we know these patients all

develop low-level pulmonary hypertension and if they have that pulmonary hypertension, again, this data demonstrates poor outcomes on these Kaplan-Meier survival curves.

We know that pulmonary function testing is very important in predicting outcomes. We know that most patients with IPF will exhibit restrictive disease marked by a decrease in their forced vital capacity. We know that the FEV_1/FVC ratio can be normal to increased, representing an increased elastic recoil. We know that the diffusing capacity representing loss in the capillary bed will be reduced and the total lung capacity will be reduced. We know that patients with concurrent emphysema may have a counter balance to that, leading to normalization of lung volumes and spirometry, but both attacking the DLCO. Right, emphysema makes the lungs big and pulmonary fibrosis makes the lungs small, and the result is that you may end up at an even number, but both will reduce the lung capacity.

We know that a low baseline FVC, we know that a decline in FVC, that a low DLCO, and a worsening 6-minute walk are all associated with decreased survival.

Probably the most powerful predictors we have are dynamic ones, in other words, change over time. If FVC gets worse over time, this is Collard's data, now being a decade and a half old, that demonstrated that as patients lost

FVC, their Kaplan-Meier's clearly demonstrated worse outcomes.

Similarly, this is the Latsi data, again about a decade and a half old. As patients lost function in their DLCO and dropped their value over a 6- to 12-month period, they also demonstrated poorer outcomes. Now, both of these are small patient numbers, 20 and 21 in this particular study, [and] the previous data was also of similar size. But the reality is the data has been proven numerous times at this point for numerous datasets.
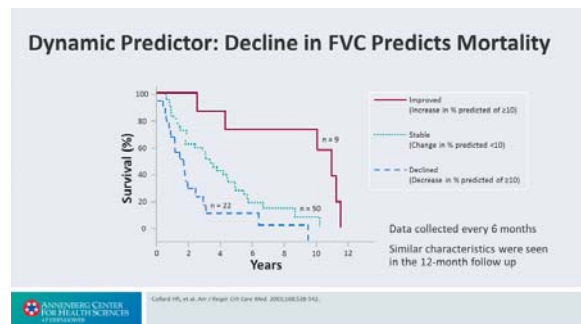
All right, what's unusual about this disease is this is an entity that is not yet molecularly defined. What do I mean by that? We don't take a hemoglobin A1C to define it. Ultimately, we have a multidisciplinary discussion for agreement as to what this idiopathic entity it is.

This study by Kevin Flaherty, a number of years ago, is still the gold standard for how we approach the diagnosis, in which he took a group of clinicians and radiologists and pathologists. And in step 1, he simply asked them what the diagnosis was in a separate room and then put them together to discuss it, and then finally added pieces of data to see what the influence was in the consensus of diagnosis.

It should be no surprise that when you take a look at the Kappa statistic, which is the level [of] agreement among clinicians, radiologists, and pathologists, that they simply improved as people got more data and talked to each other, which is what the slide really shows you.

The most important steps aren't between 1 and 2, this is where people kind of came together a bit. It's really between steps 3 and 5 when the groups started to add information and discuss it in a room together, the level of agreement improved across the board both between academic clinicians, academic radiologists, and academic pathologists.
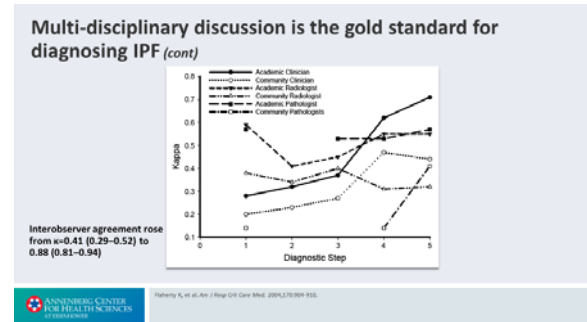
What's fascinating is there was recent data published in the paper just a few months ago that demonstrated that you didn't need to be an academician to be smart at this. It really had to do with how old you were and how many cases you had seen. And so the people who do a lot of this get very good at it, and particularly when they talk to their colleagues.
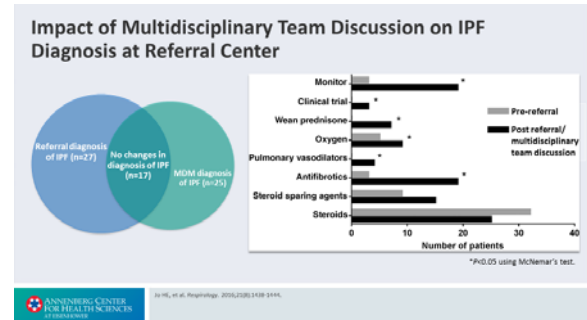
The first step is to realize that what we see as clinicians matters in this diagnosis that still uses a multidisciplinary discussion. And that the history and physical is where we start and then how we incorporate the pathology and radiology into that process changes our approach to a final diagnosis, and into the treatment and management of these patients.

As we integrate that data, looking at the impact of a multidisciplinary team discussion on the IPF diagnosis, this study by Jo et al really helps demonstrate the impact. What we see is that once patients were referred to a center, the multidisciplinary meeting really changed the diagnosis in a significant number of patients. More importantly, it increased the number of monitoring from pre to post, increased exposure to clinical trials, increased the weaning of prednisone, increased oxygen use, increased pulmonary vasodilator use, antifibrotics, and increased steroid-sparing agents, while reducing overall steroid use.

Treatment Principles

Steven Nathan, MD: When a patient has any interstitial lung disease, disease progression can be quite common, it can be unpredictable, it can be insidious, it can be sudden. The course of the disease can be quite variable. The major goals of treatment are firstly to remove any potential offending agents where they're known. For example, if a patient's a smoker, they should stop smoking. If a patient is suspected of having chronic hypersensitivity pneumonitis and has a bird in the house, then the bird needs to move out of the house or the patient needs to move out of the house or keep the bird in the house, but the patient needs to get away from the bird.

Early diagnosis and aggressive suppression of any acute or chronic inflammation also becomes very important as well. Some of these interstitial lung diseases are characterized by variable amounts of inflammation, whereas others are characterized mostly by fibrosis. If and when the patient develops evidence of hypoxemia, this should also be addressed with supplemental oxygen because hypoxemia, aside from giving the patient increased symptoms, can cause downstream consequences of pulmonary hypertension. Once patients develop pulmonary hypertension they can develop right

heart failure and their prognosis can be significantly worse.

The course of the ILDs, and especially IPF, is very unpredictable. The patients can stay stable for a period of time; they can have sudden, acute deteriorations or acute exacerbations. They can have a stair-step pattern of progression. It becomes very difficult to predict in an individual patient what their course is going to be.
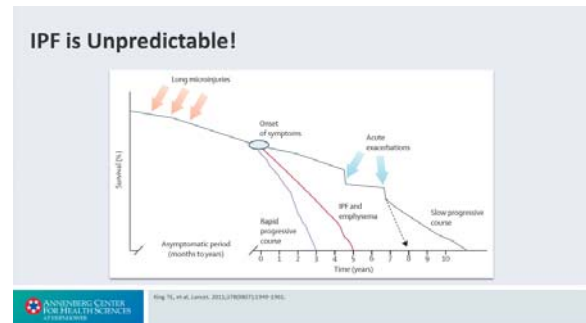
It's very important for primary care providers to be aware of interstitial lung disease, and IPF in particular, since it makes intuitive sense that the earlier one makes a diagnosis, the earlier one can intervene and the greater the likelihood of success in terms of maintaining patients' lung function and affecting their outcomes in terms of maintaining or improving their quality of life, and potentially maintaining and improving their survival.
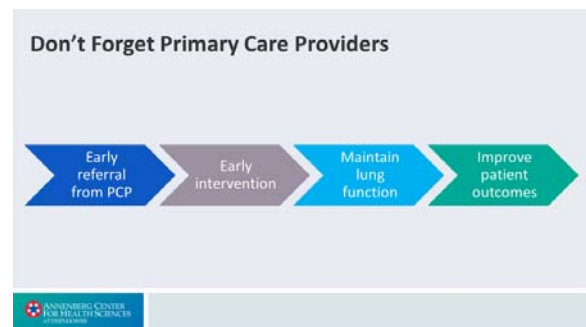
When we take care of these patients, we shouldn't only focus on the lung disease aspect

of their condition, and focus on treating their ILD or IPF, but we need to take a holistic approach to the management of these patients. This includes being aware of and screening for various comorbidities. And comorbidities may be common in these patients especially because they're elderly, but aside from this, patients with IPF, in particular—even if you account for age, smoking history—have a higher incidence of various comorbidities including obstructive sleep apnea, concomitant COPD, lung neoplasms, gastroesophageal reflux disease, thromboembolic disease, coronary artery disease.

It's very important for the pulmonologist to work in conjunction with the patient's primary care physician in screening for these comorbidities, and managing them, should they become manifest. At various stages of the disease progression, it becomes appropriate to get other resources in place, such as palliative care, to manage patient symptoms, and if the patients progress to a point where they have hypoxic respiratory failure, and they're not transplant candidates and everything else has been tried, then hospice care can become important as well.

In terms of treatment options for the various forms of ILD, and I'm not talking about IPF now—that's managed quite differently. Steroids can be used, especially if there's ongoing evidence of alveolitis or inflammation. However, in the ILDs other than IPF, there haven't been many, good, randomized, controlled, clinical trials to guide us in terms of how to treat these patients.

For any individual patient, when a clinician is faced with a patient who has interstitial lung disease, they have to balance the safety of any intervention vs the likelihood of a potential benefit. Generally, for most ILDs, we use some form of immunosuppression when we do offer therapy. Some of the agents that may be used include mycophenolate, azathioprine, cyclophosphamide. The most common one

these days being used is mycophenolate, however. Other agents have also been tried, including methotrexate, colchicine, penicillamine, cyclosporine, tacrolimus, but the data supporting this is very skimpy.

It's very important to differentiate IPF from other forms of interstitial lung disease. Some forms of interstitial lung disease may be characterized by inflammation. If there is evidence of inflammation, treatment options include steroids, as well as other immunosuppressive agents. Most typically, these days, it'll be mycophenolate. Patients need to be treated and followed very closely for any side effects and response to therapy. If patients do not respond to therapy with immunosuppressive agents and steroids, then one has to gauge on a case-by-case basis whether the utility, whether there's any usefulness in terms of continuing this, and balancing the safety vs the benefit, down the road, of these medications, which in some cases can have significant side effects.

If patients have interstitial lung disease other than IPF, and if the interstitial lung disease is characterized by any element of inflammation, then the treatment options usually include steroid therapy given with other immunosuppressive agents. Some of them that have been used include mycophenolate, cyclophosphamide, and azathioprine. Other ones that have more historical interest with no data to support their use are colchicine, penicillamine, cyclosporine, and tacrolimus, as well as methotrexate.

Typically, if patients have interstitial lung disease, we'll treat them with a combination of mycophenolate, usually, and steroids. We have to follow these patients closely and gauge them for clinical response or stability and decisions have to be made in terms of the utility of continuing these therapies, and for how long we should continue these therapies on a case-by-case basis. Unfortunately, we don't have many or any randomized, controlled, clinical

trials, to guide us in the treatment of patients with various forms of interstitial lung disease. There are some studies in CTD-ILD, specifically scleroderma, attesting to the utility of both cyclophosphamide and, more recently, mycophenolate, but whether or not the benefits of these medications are sustained beyond 1 or 2 years is uncertain. That's why one has to look at each patient individually and decide whether or not to continue therapy based on the benefit vs the safety and side effect profile of each of these medications.

There's a lot more data in IPF and there's a lot more studies that have been done in IPF. The IFIGENIA study looked at the use N-acetylcysteine and its effects on the rate of loss of forced vital capacity (FVC) over the course of 12 months. This study was done primarily in Europe and it did show that N-acetylcysteine appeared to be a useful therapy that delayed progression of disease. The problem with this study was that the placebo arm was on what was at that time regarded as standard of care therapy, which include azathioprine and prednisone. One of the criticisms of the study was that there wasn't a true placebo arm, and we didn't know, and there wasn't good data in terms of what azathioprine and prednisone did for the lungs in patients with IPF.

High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

IFIGENIA Study
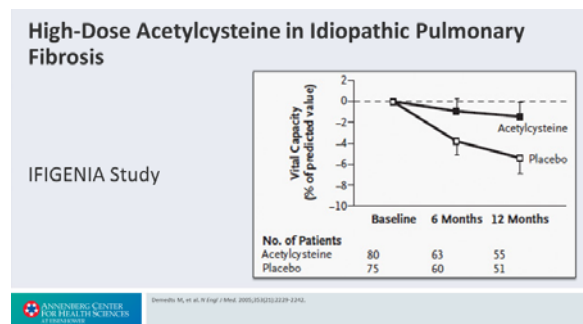
This was the underpinnings of the PANTHER Study. This was an NIH-sponsored study done by a network of clinical scientists throughout the United States, which attempted to answer 2 questions at the same time. The first question was: What is the role of N-acetylcysteine? The second question was: What is the role of prednisone and azathioprine? There were 3 arms to this study. The first arm included triple therapy with prednisone, azathioprine, and N-acetylcysteine. The second arm included N-acetylcysteine alone. The third arm was placebo.

The study was followed closely by the data safety monitoring committee who, at one point, noted that one group was doing particularly worse. That group happened to be the group who was getting triple therapy with prednisone, azathioprine, and N-acetylcysteine. The study was halted and a paper was published fairly expeditiously to warn people about the deleterious effects of combination therapy with prednisone, azathioprine, and N-acetylcysteine. Prednisone and azathioprine are now contra-indicated in patients who have IPF, whereas these medications might, and still are, used in other forms of interstitial lung disease. Hence, the importance and the critical aspect of making accurate diagnosis with IPF vs other forms of interstitial lung disease.

Prednisone, Azathioprine, and *N*-Acetylcysteine for IPF (PANTHER-IPF): Harm and No Benefit
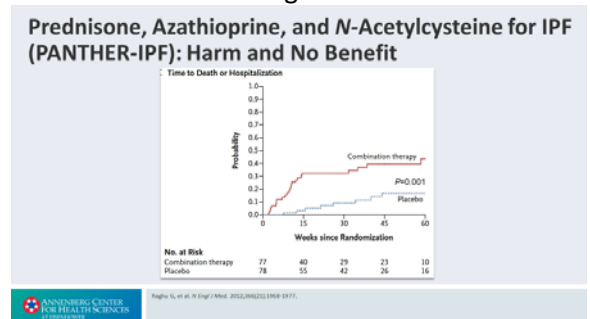
The PANTHER Study, this was continued as a 2-arm study comparing N-acetylcysteine to placebo, and this turned out to be negative. It wasn't harmful, but it appeared that N-acetylcysteine, or NAC in isolation, was not a useful therapy in terms of delaying loss of lung function in patients with IPF over the course of this particular study.

Acetylcysteine in IPF: No Preservation of FVC

PANTHER-IPF 2-Arm Study

There's been a seismic shift in the treatment paradigm for patients who have interstitial lung disease, whereas previously everyone was treated the same, and IPF, another form of interstitial pneumonitis, connective tissue disease, or whatever form of interstitial lung disease they had, patients generally, historically, were treated with immunosuppressive therapy. Now, IPF is not treated with immunosuppressive therapy. In fact, as shown through the PANTHER Study, azathioprine and prednisone, in particular, can be harmful to these patients. IPF we now treat with the antifibrotics. We're in the era of antifibrotic therapies. Whereas these other forms of interstitial lung disease might still be candidates for immunosuppressive therapy, either with azathioprine and prednisone, [or] more commonly these days, with mycophenolate and prednisone.

Treatment Paradigm Shift

Let's move onto the clinical trials that resulted in the antifibrotic therapies being approved. The first one we'll discuss is pirfenidone. Pirfenidone was initially studied in 2 distinct or disparate clinical trials, the 2 CAPACITY studies. The reason that there were 2 clinical phase 3 studies was that the FDA likes to see 2 randomized, controlled studies—phase 3 studies—in order to provide an approval for a particular drug.

What was found from the 2 capacity studies: in study 004 we had a positive result with a slowing in the rate of decline of the FVC over the course of 72 weeks in the pirfenidone arm vs the placebo arm. However, in study 006, the 2 curves came together and there wasn't a difference at 72 weeks in terms of the rate of decline in FVC. What you can see from the pooled data was that if you looked at both studies together, it would have been a positive clinical trial. However, the FDA at the time said, "One study positive. One study negative. You need to go back and do a third study, a so-called tie breaker study."

Pirfenidone in Patients with IPF (CAPACITY)

This was the underpinnings and foundation for the ASCEND study shown over here, a phase 3 trial of pirfenidone in patients with IPF, which showed definitively that pirfenidone did slow the rate of progression of disease as shown and demonstrated here, the FVC, as well as improving progression free survival.

Pirfenidone in Patients with IPF (ASCEND)

Pirfenidone does come with side effects. The major side effects are GI, nausea, diarrhea, as well as skin rash and photosensitivity. Those are the 2 major side effects that can be seen with pirfenidone, but not everyone necessarily gets them.

If one looks at the pooled data of the 3 clinical trials, the 2 CAPACITY studies and ASCEND, and look at change in the FVC, this is a positive study. Putting them all together and over a thousand patients, 1256 patients or thereabout, it was a positive signal seen in terms of the change in the FVC.
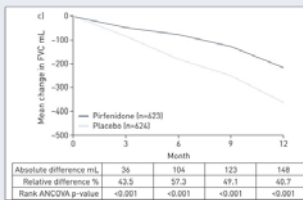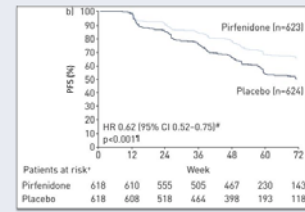

Looking at progression free survival, which was a composite of either a 10% decline in the FVC, a 50-meter decrease in the walk distance, or death, it did appear that patients treated with pirfenidone did significantly better than patients who were in the placebo arm of these 3 clinical studies.

The second antifibrotic, which is nintedanib, and this *particular paper* was in the same issue of the *New England Journal of Medicine* as was the results of the ASCEND study.

What was shown with nintedanib was very similar to what I showed already with pirfenidone, that it slowed the rate of loss of lung function, specifically the FVC over the course of 52 weeks and there was the same signal seen from the 2 studies that were done for nintedanib, INPULSIS-1 and INPULSIS-2. This was actually very similar to what was seen in the phase 2 study, which was known as the TOMORROW Study.
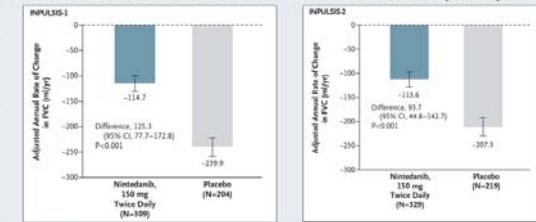
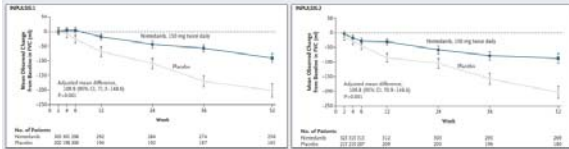Also seen over here, the curves come apart actually quite early, and this attests to the early implementation of therapy. The earlier one can start patients on therapy, the earlier there can be preservation of lung function for both nintedanib as well as for pirfenidone.

Benefit of Nintedanib on FVC Appears Early

Another endpoint that was looked at in the INPULSIS studies was the time to first acute exacerbation. There was a positive signal here as well. It did appear that nintedanib resulted in a delay to the time for an acute exacerbation of the disease.

Nintedanib Reduced Time to First Acute Exacerbation (Investigator-reported): INPULSIS Pooled
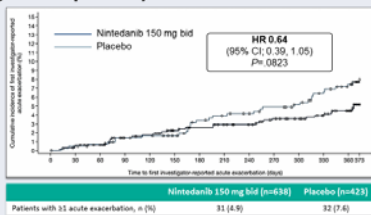
As with pirfenidone, there are side effects associated with nintedanib. These are mostly GI, once again, most specifically diarrhea, which can affect about two-thirds of patients.

INPULSIS-1 and -2: GI-related Events Were More Common in the Nintedanib Group

	INPULSIS-1		INPULSIS-2	
	Nintedanib (n=309)	Placebo (n=204)	Nintedanib (n=329)	Placebo (n=219)
GI adverse event leading to discontinuation	26 (8.4%)	3 (1.5%)	21 (6.4%)	2 (0.9%)
Diarrhea	190 (61.5%)	38 (18.6%)	208 (63.2%)	40 (18.3%)
Nausea	70 (22.7%)	12 (5.9%)	86 (26.1%)	16 (7.3%)
Vomiting	40 (12.9%)	4 (2.0%)	34 (10.3%)	7 (3.2%)

Very similar to what I showed you with the pooled result from the 3 pirfenidone studies, here we see the pooled results from the 3 nintedanib studies, TOMORROW Study, and the 2 INPULSIS studies, showing a significant

difference in the rate of decrement in the FVC over the course of 52 weeks.

Nintedanib Slowed Reduction in FVC: Pooled Results of TOMORROW + INPULSIS Trials
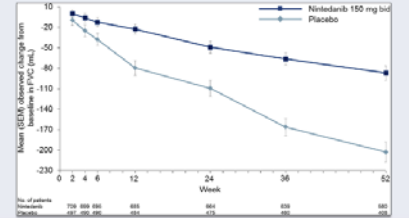
Similarly, pooled data and the effects on acute exacerbations, once again a significant effect in delaying the time to an acute exacerbation from nintedanib.

Nintedanib Reduced Time to First Acute Exacerbation (Investigator-reported): Pooled Results of TOMORROW + INPULSIS Trials
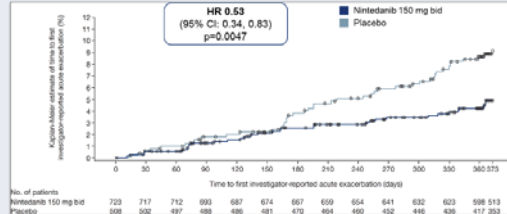
Side effect profile of the 2 drugs. Both of them can have GI side effects. As mentioned, pirfenidone can cause rash or photosensitivity. There's a very small signal of myocardial infarction and bleeding events in patients with nintedanib. Both drugs can cause a mild transaminitis, and following LFTs is very important for both of these agents.

When one decides between these drugs, one has to weigh the benefits as well as the risks and potential adverse events. The nice thing about having 2 antifibrotics is that we have a choice. Typically, what I do in my clinical practice is to decide on the antifibrotic that is most likely to be well tolerated by the patient. For example, and I'll give you 2 extreme examples. One, if I have a patient who likes to play golf 6 days a week, then probably steer clear of pirfenidone. If I have a patient who's on

anticoagulation therapy for whatever reason, then probably steer clear of nintedanib and direct the patient more to pirfenidone. There is no direct comparison of these 2 different drugs. Taking all the results together does appear that they have somewhat equivalent effects in treating patients with IPF. I think the important thing is to make an accurate diagnosis and offer the patients the option of going on one of the antifibrotic therapies.

One of the things that can happen with IPF is it can be complicated by the development of pulmonary hypertension. There's a lot of interest in looking at some of these pulmonary arterial hypertension (PAH) medications that have been approved, and whether or not they might have any benefit in patients with IPF who develop pulmonary hypertension.

The STEP IPF study was one such study that didn't look specifically for patients with pulmonary hypertension, but was certainly enriched for patients with pulmonary hypertension since the one inclusion criteria was a diffusing capacity less than 35% of predicted. The study was a negative study based on the primary endpoint, which was an improvement in the walk distance of 20% or more. It didn't reach statistical significance. However, various secondary endpoints suggested that there might be some benefit to sildenafil therapy. Specifically, there was a difference in the shortness of breath questionnaire, quality of life measures, as well

as the single breath diffusing capacity. There was the suggestion of a signal of a mortality benefit. However, the numbers were extremely small and one should look at this with some circumspection. I believe the numbers were 11 deaths in the one arm, vs 4 deaths in the other arm. It was a *P* value of .07, so certainly no claim that sildenafil affects mortality. There are, however, ongoing clinical trials looking at pulmonary hypertension medications in patients with IPF. Hopefully we'll hear more about this in the future.

STEP-IPF: Sildenafil Does Not Improve Walking Distance But Significantly Improves Some Secondary Outcomes

Endpoint	Sildenafil	Placebo	Absolute difference	P value
Primary Endpoint				
Improved Walking Distance ≥20%	10%	7%	—	0.39
Secondary Endpoints				
UCSD SOBQ	0.22	6.81	-6.58	0.006
SGRQ	-1.64	2.45	-4.08	0.01
DL_{CO}, % pred	-0.33	-1.87	1.55	0.04
Mortality	5%	13%		0.07

DL_{CO}, diffusing capacity for carbon monoxide; SGRQ, St. George's Respiratory Questionnaire; UCSD SOBQ, UCSD Shortness of Breath Questionnaire.

Anticoagulation has also been thought to potentially be a treatment modality in patients with IPF. There's evidence of thrombin formation within alveoli, and this has been looked at in the context of the ACE study where warfarin was studied in a randomized, clinical, controlled setting. This was one of the NIH IPF networks clinical studies. Unfortunately, what was shown was that not only was there no benefit, but there was also increased risk and increased mortality in patients who were treated with warfarin. Warfarin is contraindicated in patients with IPF, unless patients have a primary indication for it. If a patient has atrial fibrillation (A fib), has a prosthetic valve, or other reason to be on warfarin, this certainly should not be withheld, but as a primarily treatment modality for IPF, this is not indicated.

ACE-IPF: Warfarin Offers No Benefit But Increases Mortality Risk

Primary Endpoint*: No benefit | All-Cause Mortality: ↑ Risk with Warfarin | All-Cause Mortality and All-Cause Hospitalization: ↑ Risk with Warfarin

*Composite of time to death, hospitalization (nonbleeding, nonelective), ≥10% absolute decline in forced vital capacity.

Noth I, et al. Am J Respir Crit Care Med. 2012;186(1):88-95.
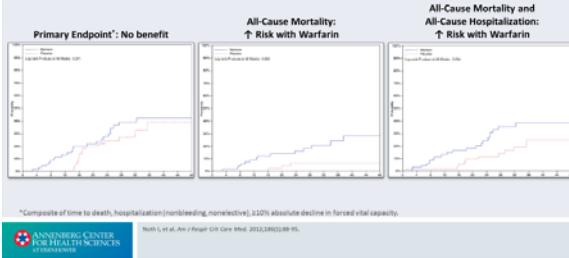
Our governing bodies, including the ATS and ERS, have come out at various times with recommendations with regards to how we should treat or not treat IPF. They have come out with 3 categories: strong recommendation against, conditional recommendation against, and conditional recommendation for. There's nothing that has been deemed to constitute a strong recommendation for. The highest recommendation we have is a conditional recommendation for use of the 2 antifibrotics, either nintedanib or pirfenidone, as well as antacid therapy. Although the data supporting antacid therapy is somewhat weak and this remains a controversial area.

ATS/ERS/JRS/ALAT Recommendations for Pharmacologic Treatment for IPF

Strong recommendation against	Conditional recommendation against	Conditional recommendation for
• Anticoagulation (warfarin)*§ • Imatinib*§ • Combination prednisone, azathioprine§, and N-acetylcysteine§* • Selective endothelin receptor antagonist (ambrisentan§)*	• N-acetylcysteine§ monotherapy • Phosphodiesterase-5 inhibitor (sildenafil)*§ • Dual endothelin receptor antagonists (macitentan§, bosentan§)*	• Nintedanib† • Pirfenidone† • Antacid therapy*§

*Low confidence in effect estimates; †Moderate confidence in effect estimates; §Not approved for IPF in the United States

Raghu G, et al. Am J Respir Crit Care Med. 2015;192(2):e3-19.

For patients who progress despite the option of therapy and if they do not have significant comorbidities and if they are young enough, then they might be candidates for lung transplantation. The age cutoff depends on individual centers. Some have a cutoff of 70. Some centers will go as high as 75. There are even a few patients who are older than 75 who have been transplanted.

The time to transplant patients with IPF, or any condition for that matter, is when the risk of

mortality from the underlying primary disease is greater than the risk of mortality from having a lung transplant.

When we look at patients as potential transplant candidates, we look at contraindications as well. There's a number of things in actual effect that may constitute a contraindication: Various malignancies, significant other end organ dysfunction, uncorrected or uncontrolled atherosclerotic disease, medical instability, bleeding diathesis, chronic infections with virulent resistant microbes. These might all be contraindications, and the contraindications actually vary, as well, from center to center. Some centers, especially the larger centers who have greater numbers, might be more inclined to do patients who are perhaps regarded as more marginal candidates at other centers.

The list carries on in terms of other contraindications, chest wall abnormalities, obesity (BMI greater than 35 kg/m^2), psychosocial issues can be contraindications. Patients have to have a good support system, and have to have good rehab potential as well.

Relative contraindications are shown here. Age, once again, obesity, malnutrition, osteoporosis. Extensive prior to surgery or lung resection, they're really not a contraindication these days, and in actual effect we've taken a good number of patients off mechanical ventilation or extracorporeal membrane oxygenation (ECMO) and offered them transplants, too. This, once again, becomes case by case.

The survival after transplant varies. It's not the panacea. It is like trading one disease for another. If you look at the survival of patients with IPF, here shown as IIP, interpathic interstitial pneumonia, it tends to be worse than other disease conditions such as cystic fibrosis. It might be a function of age or the underlying lung condition. As mentioned, IPF is a disease of the elderly, whereas cystic fibrosis (CF) patients tend to be in their 20s, 30s, maybe

40s when they get a transplant. Whether it's underlying disease, or age, that factors into this difference in survival, is a little bit uncertain.

We like to think we are getting better with transplant as the years roll by and as we go through different eras. We're not yet where our cardiac colleagues or our hepatology colleagues are in terms of survival. The reason that we aren't improving survival as much as we would like is because we're taking sicker patients and older patients at the same time. Hopefully we'll make further inroads in terms of long-term survival in the coming years.

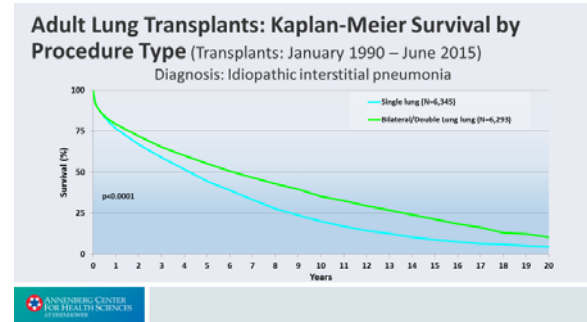
If one looks at IIP or IPF, there is data to suggest that patients who get bilateral lung transplants do better than patients who have single lung transplants. However, one needs to be cautious when one looks at a survival curve like this, because there's a certain bias here. Patients who get bilaterals, once again, tend to be younger and perhaps more robust. Patients who get singles tend to be older and maybe a little less robust. When one controls for all

these other factors and does multivariate analysis, it does appear that survivals tend to be fairly similar with singles vs bilaterals in patients with IPF.

In summary, it's important once again to make the distinction between IPF and other forms of interstitial lung disease, because the treatments are very different, especially with availability of the antifibrotic therapies, which have been available for almost 4 years now. Lung transplant is an option for select patients provided they do not have a contraindication to having a lung transplant. Thank you for your time and attention.
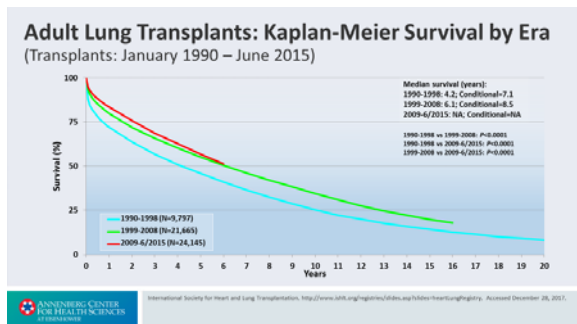
Treating Acute Exacerbations

Steven Nathan, MD: In this first slide you see a very nice cartoon depiction of the pathogenesis of IPF and how this might be complicated by an acute exacerbation. What we know about IPF is that there's initially some epithelial disruption. You have the fibroblast coming in. These might transform to myofibroblasts, then later collagen. Collagen is the scaffold for fibrotic changes and progressive fibrosis, which results ultimately in respiratory failure.

Slow vs Fast Disease Progression in IPF

There are many reasons or predisposing factors for IPF. There might be a genetic predisposition in some patients, environmental factors may play a role, behavioral factors such as smoking might play a role in setting off the process, and certainly aging plays a role as well.

Slow vs Fast Disease Progression in IPF
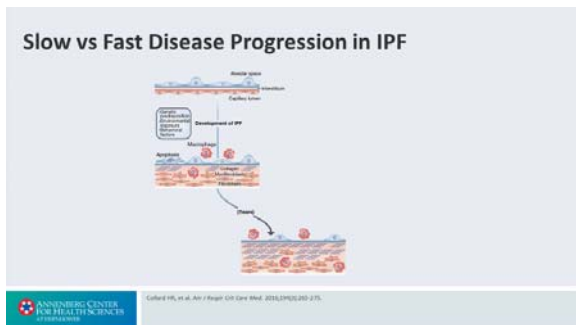
Every patient with IPF is at risk of developing an acute exacerbation. Maybe about 10% to 15% of IPF patients will develop acute exacerbations. There might be various precipitating factors for an acute exacerbation, including acid reflux, various infections might precipitate an acute exacerbation, mechanical factors such as stretch might precipitate an acute exacerbation. There's also anecdotal evidence and a suggestion that very high fraction of inspired oxygen (FiO2) might precipitate an acute exacerbation.

Slow vs Fast Disease Progression in IPF

What happens, though, is that a separate or different and distinct pathologic process is set in place. It looks like acute resp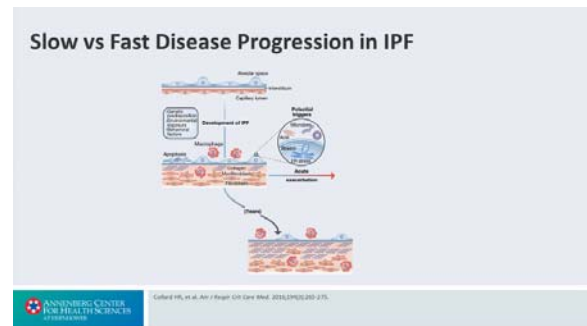iratory syndrome (ARS) basically. You have hyaline membrane formation, patients manifest on CT and chest x-ray with diffuse alveolar infiltrates, superimposed over the interstitial lung disease that characterizes IPF.

Slow vs Fast Disease Progression in IPF
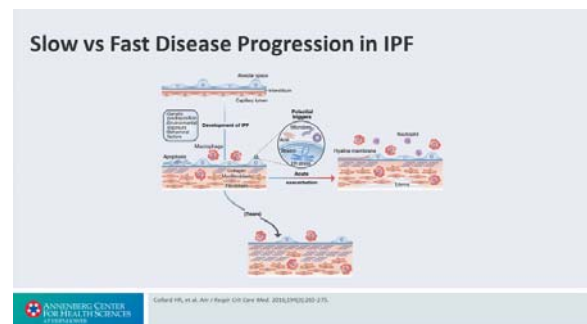
Generally, the prognosis after the onset of an acute exacerbation tends to be quite poor. Acute exacerbations can happen at any time during the course of disease. Patients can have relatively well-preserved lung function, they might have more advanced disease, and sometimes, in actual effect, acute exacerbations can be the first manifestation of the underlying IPF.

Slow vs Fast Disease Progression in IPF

There are various factors associated with increased risk of mortality in patients with IPF. Baseline factors that can be associated with increased risk of mortality include: Level of dyspnea, the lower the diffusing capacity, the worse the prognosis, the more the patient desaturates, the worse the prognosis, the greater the extent of honeycombing on HRCT, the worse the prognosis, and similarly for pulmonary hypertension. If patients develop pulmonary hypertension this generally portends a significantly worse outcome.

There are also longitudinal factors that can portend to worse outcome, so if patients return to the clinic complaining of increasing shortness of breath, increasing dyspnea on exertion, if they have a 10% or more reduction in the FVC or 15% more reduction in the DL_{CO}, and/or worsening fibrosis on HRCT, all of these things longitudinally will portend a worse prognosis for patients with IPF.

When patients present with increased shortness of breath in the context of IPF, the clinician is often left with the decision as to whether or not this is deterioration or progression of the disease, or if, in actual effect, they are having an acute exacerbation of the IPF. When patients present with an acute exacerbation, generally the increase in dyspnea is usually less than 1 month in duration. It's a subacute onset.

What we focus on is ruling out some kind of extraparenchymal cause of their shortness of breath. Do they have coronary artery disease, for example, that is now manifesting with shortness of breath? We know that patients with IPF are at higher risk of having an acute coronary syndrome. Other things might be a pneumothorax or a pleural effusion or pulmonary embolism that can manifest as acute onset or subacute onset of shortness of breath. Typically, what characterizes an acute exacerbation is the presence of ground glass

infiltrates, or even consolidation that is sometimes evident on chest x-ray, but is more commonly evident on chest CT. Chest x-rays are usually not that helpful in the context of an acute exacerbation. When we see this, then, it's incumbent on us to try to exclude things that might have precipitated this.

We are left with distinguishing between a triggered acute exacerbation or an idiopathic acute exacerbation. Previously if something was triggered by infection we wouldn't regard it as acute exacerbation, but there's been a fairly recent change in how we approach acute exacerbation where it's more encompassing, so that even if there's a known infection that sets off the acute exacerbation it's still regarded as an acute exacerbation of the underlying IPF.

The diagnostic criteria for an acute exacerbation of IPF are unexplained worsening of shortness of breath within 30 days, new changes on the HRCT that I mentioned already in terms of the bilateral, usually bilateral ground glass infiltrates, sometimes consolidation and on the backdrop of a UIP pattern or a patient with known IPF. Typically, we try to exclude a pulmonary infection. We either get a sputum culture; if the patient's intubated we'll get a bronchoalveolar lavage. Even if we find a bug down there, in the latest paradigm we'll note the bug, we'll treat the bug, but we'll still regard it as an acute exacerbation of the disease. We still have to exclude other causes of decompensation, including left heart failure,

pulmonary embolism, pneumothorax, and other identifiable causes of acute lung injury.

The treatment of acute exacerbations is generally not very good. Preventative strategies include the implementation of antifibrotic therapy prior to the development of the acute exacerbation. Nintedanib specifically has been shown to delay the time to acute exacerbation and there's also evidence for pirfenidone from some of the older Japanese studies, that this might have a favorable impact on the subsequent development of acute exacerbations. Typically, what is implemented once a patient has an acute exacerbation include various medications that have been tried, but we don't have any solid evidence that any of these drugs actually work. We'll use steroids, cyclophosphamide's been used, cyclosporine has been used, hemofiltration or hemoperfusion has been used, rituximab, tacrolimus, various things have been used, but there's no good evidence that any of these have any effect.

You'll also use high-dose steroids. There's no good guidance about this, but we all do it. Whether this helps or not is very uncertain. Some patients are candidates have gone to mechanical ventilation, but generally mechanical ventilation, as well as ECMO, is only recommended for those patients who are being bridged to transplantation. If a patient with IPF develops an acute exacerbation requiring mechanical ventilation, then the prognosis is typically quite dismal and we'll usually talk to the patient and/or their families about more comfort care measures rather than going the route of mechanical ventilation, but definitely ECMO should only be reserved for those patients who are being bridged to lung transplantation.
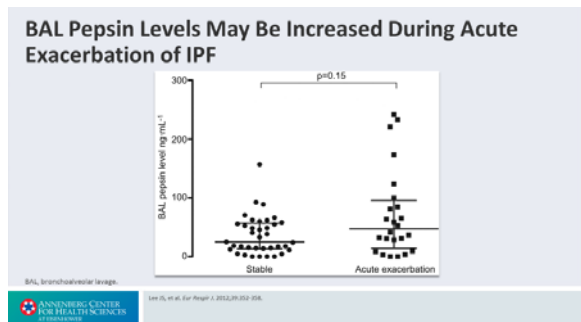

Treatment of Acute Exacerbations

Don't forget to also address comorbidities in the context of patients who present with acute exacerbations. I mentioned that things such as coronary artery disease, heart failure, venous thromboembolism (VTE) might all manifest with increased shortness of breath. Don't forget about that. Don't forget about providing psychosocial support, not only for the patient, but also for the family as well. It always helps to have a multidisciplinary care team in place to help to provide care to the patient and to take care of all manifestations of the disease, as well as some of the downstream complications that can ensue in patients who have IPF, especially as they head towards the end stages of their disease. It's very helpful to have palliative care and hospice services involved as well.

This slide goes back to the etiology of an acute exacerbation showing that some patients who develop acute exacerbations have higher bronchoalveolar lavage (BAL) pepsin levels implicating perhaps that gastroesophageal reflux disease may have a role in some of these patients in terms of precipitating an acute exacerbation of the underlying IPF.
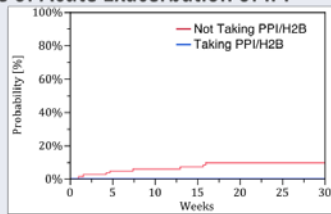

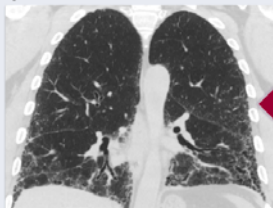BAL Pepsin Levels May Be Increased During Acute Exacerbation of IPF

Whether or not proton pump inhibitors (PPIs) or histamine type 2 (H2) blockers have a role in preventing acute exacerbations, well, there's some data from some post hoc analyses that maybe these do, but this still remains to be validated in prospective clinical trials.

When should a patient with IPF be considered for transplant referral? This is an easy one. They should be considered for transplant referral at the time of diagnosis, for the very reason of acute exacerbations. Acute exacerbations can happen in patients who are asymptomatic, who have normal levels of lung function, and usually this is something that is recommended because we want to put the safety net of a transplant evaluation in place in case a patient has a sudden deterioration related to an acute exacerbation.

We talk about a window of opportunity for transplant, for placing patients on the transplant list. We don't want to put them on the list when they're too early or not sick enough, and we don't want to wait until they're too sick to warrant transplantation.

The back end of this window admittedly has grown through the years where we'll now transplant patients on mechanical ventilation and take patients off ECMO and transplant them as well. Sometimes patients with IPF can whiz through this window quite quickly, especially if they're in the process of having an acute exacerbation. Hence, once again, the need for early referral for transplant evaluation. Transplant evaluation doesn't necessarily mean the patient will be placed on the list right away, but should they have an acute exacerbation, it makes it much easier to put them on the list more expeditiously and try and salvage them with a lung transplant.

Once again, the timing of referral is at the time of diagnosis. Timing of listing takes a discussion between the patient and their transplant pulmonologist. Here are some guidelines if the patient has deterioration: A 10% drop in their FVC, a significant drop in the DL_{CO}, if they have increasing oxygen needs, if they're hospitalized. These might all be reasons to go ahead and proceed with listing them for lung transplantation.

In summary, acute exacerbations are a complication of IPF. That's one of the reasons that some patients who have normal lung function might succumb from their disease relatively quickly or relatively early. We need to have a high index of suspicion for acute exacerbations if patients complain of increasing shortness of breath. They should be seen early, and they should perhaps be brought into the hospital for management of their acute exacerbations. Our management, unfortunately, for acute exacerbations is not very good. We use steroids, we use antibiotics, we try and diurese them, but the mortality remains very high, in excess of 80% and

certainly, if patients are transplant candidates and they're in the process of having an acute exacerbation, they need to be put on the list pretty expeditiously. ECMO, mechanical ventilation, are measures that should be reserved only for patients who are being bridged to lung transplantation. Thank you for your attention.

Palliative Care

Steven Nathan, MD: Interstitial lung disease is characterized by a major reduction in patients' quality of life, especially as the disease progresses. And aside from medical therapies, there's a lot that can be done for the patient in terms of palliating their symptoms to maintain or possibly improve their quality of life. This usually involves a multidisciplinary approach, social workers, nurse coordinators, but especially pulmonary rehab specialists are very important.

What happens with IPF and for any lung disease that causes progressive shortness of breath is that as the patients develop increasing dyspnea on exertion, they do less; and when they do less, they become more deconditioned. They have more easy fatiguability; they're less active.

That results in social isolation. Some of these patients are embarrassed perhaps to go out with their supplemental oxygen and this leads to anxiety, depression, and a reduced sense of emotional well-being. This is a vicious, downhill spiral that can affect many of the patients with interstitial lung disease, and IPF in particular.
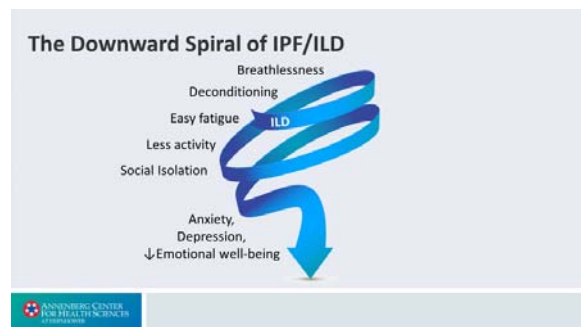
One of the goals or some of the goals of a pulmonary rehab program is to reverse this downhill spiral by getting the patients to exercise, to recondition them, to reduce their shortness of breath, to empower the patient to take control of their disease and its manifestation. I've had many patients go through pulmonary rehab who have interstitial lung disease and by far and away the majority of them do benefit significantly and have an improved quality of life as a result of this. Pulmonary rehab also provides education for the patients, as well as provides them with a support group. They have the opportunity to meet other people who have the same disease that they do. This is a benefit to all patients. It's a simple measure, minimal downside, but pretty much all patients with IPF will benefit from pulmonary rehab. And typically it's run by respiratory therapists, with the aid of physical therapists as well.

There have been studies looking at the utility of pulmonary rehab in patients with interstitial lung disease that have shown that pulmonary rehab will result in an increase in the 6-minute walk distance. However, it's very important for the patients to continue being active and to continue exercise to make sure that these effects are sustained over time.

As patients progress to the point that they have advanced disease requiring oxygen, they may also be candidates for lung transplant. They have to be young enough, usually less than 70 to 75, and not have significant comorbidities that might preclude them as transplant candidates. However, having a transplant is not necessarily the panacea, and transplantation does carry with it significant risk.

Exercise Training Effect on 6-Minute Walk Distance
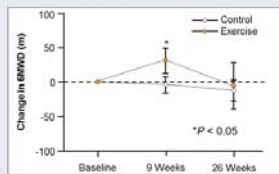
Conclusions
• Exercise training improves exercise capacity and symptoms in patients with ILD
• Benefits are not sustained at 6 months

We have Kaplan-Meier survival curves after transplantation showing that the 1-year survival is around 85%, but as you get out to perhaps 5 or 6 years, the median survival is about in that range. We are getting a little bit better with time in terms of different eras. However, transplant still carries with it significant potential mortality as well as morbidity.

Adult Lung Transplants: Kaplan-Meier Survival by Era
(Transplants: January 1990 – June 2015)
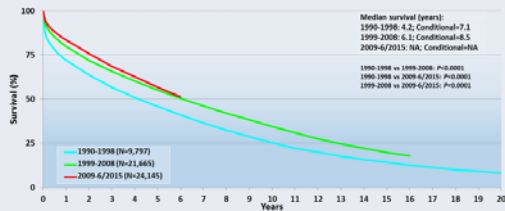
The time to consider transplantation is when the greater risk for mortality is from their primary disease and that their risk of death from their primary disease outweighs their risk of death and mortality from having a lung transplant.

When to refer patients with IPF or transplantation? Well, the belief and the teaching is that they should be referred at the time of diagnosis. Even if patients have normal lung function, they should still be referred, because of the unpredictable nature of progression of disease, yet you can have patients with well-maintained lung function, relatively asymptomatic, who might have an

acute exacerbation and might miss the window of opportunity for lung transplantation if they have not been referred earlier.

How to follow patients with IPF? Generally, we'll see them every 3 to 6 months. We'll obtain pulmonary function tests (PFTs), even if it's just spirometry, at every visit. We'll look at their 6-minute walk distance and monitor both their distance as well as their SVO_2 nadir to see if they need supplemental oxygen or not.

We're always aware of comorbidities that might complicate the course of IPF and always on the lookout for that because these might impact both their quality of life, as well as their potential outcomes. Things like coronary artery disease, thromboembolic disease, GERD, obstructive sleep apnea. These are all things or entities that can complicate or be associated with the course of patients who have IPF.

A question often comes up as to when to get or repeat the CT. Now, the HRCT is essential to make a diagnosis of IPF, but it's a little bit of a blunt instrument in terms of following the clinical course. Typically, we rely more on physiology, specifically PFTs and the 6-minute walk test to follow the course of patients with IPF. I usually will repeat a CT annually, not necessarily or so much as to follow the progression of disease, but to screen for things like lung cancer. Lung cancer is one of the comorbidities that can complicate the course of patients with IPF and it's estimated that perhaps about 10% of patients with IPF will die as a result of developing lung cancer.

In summary, lung transplantation is an option for select patients who have advanced IPF and have progressive respiratory failure. Pulmonary rehab is an essential element that should be implemented at some point in the patient's disease course, not only for patients who are transplant candidates, but for any patient with

IPF who gets to the point that they're symptomatic and become deconditioned. This is a very valuable resource that is of benefit to pretty much all patients with IPF at some point in their progression of disease. Don't forget about comorbidities. In the holistic care of these patients, comorbidities may play a significant role in their health disease status and sometimes patients with IPF will die with their IPF, rather than from their IPF. Some of the things that could cause their demise include lung cance
r and coronary artery disease. Don't forget about comorbidities. Thank you very much for your attention.

Future Directions

Imre Noth, MD: What is precision or personalized medicine? It's an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person involving their environment, genes, and treatments. They allow us to discover mechanisms and targets involved to predict outcomes in patients and to prognosticate outcomes in patients. And lastly, potentially engage in the pharmacogenomics or precision or personalized treatment approach. There are a great number of biomarkers that have been developed along this line and I'm really only going to discuss a few given our short timeframe.

I want to focus in on this study by Stuart et al, that was published in *Lancet Respiratory Medicine* a few years ago. It looked at telomere length. Telomeres are portions of the DNA that basically are your lifeline. They allow for the cell to replicate and protect it from DNA damage, and this is a bit of a damned if you do and damned if you don't. If they're very, very long they predispose you to cancers through cell immortalization. If they're very short, they predispose you to other processes, one of which is pulmonary fibrosis. In this study, what it really shows you is that the red lines were

patients with very short telomeres and those patients in 3 independent cohorts at Dallas, Chicago, and San Francisco, all had far poorer outcomes than the patients with long telomeres, suggesting there is a part to the process involving DNA damage. It speaks to the underlying genetics because we know that the telomere length is directly dependent on underlying both common and rare mutations that are involved in determining that telomere length over time.
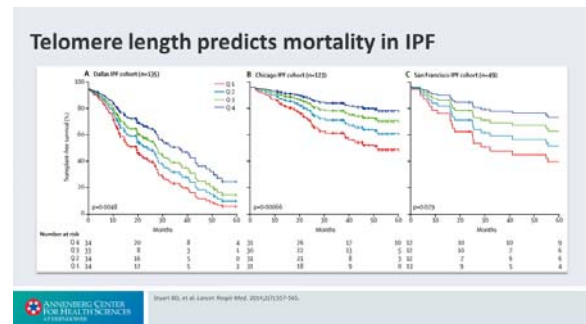
Two studies have come out looking at the underlying genetics of common variants. One was involving a Chicago consortium that demonstrated Toll interactive protein (TOLLIP) as being highly important and also predictive of outcomes in patients. The other had demonstrated the MUC5B polymorphism was also important in susceptibility and outcomes in these patients.
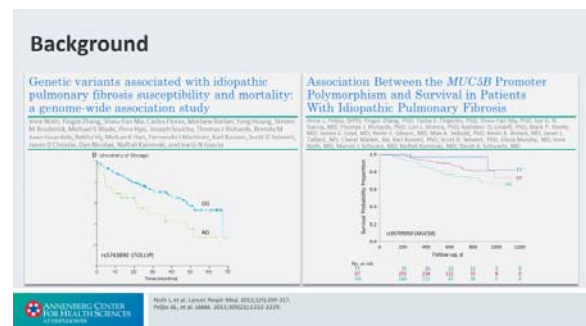

You may be familiar from a previous module regarding the PANTHER outcome dataset. This was a study looking at prednisone, azathioprine, and N-acetylcysteine vs N-acetylcysteine vs placebo in a 3-armed study that was stopped early because of the high increase in mortality

related to the triple-arm therapy. The trial was then resumed with NAC vs placebo, to take a look at the effect of NAC.

Here we have the 3 arms and the primary endpoint was supposed to be a decline in FVC, but the secondary endpoint of death, acute exacerbation, or progression.

A combination therapy had a hazard ratio that was dramatically worse than the placebo arm, suggesting that the use of immunosuppression was very dangerous.

When we took a look at the NAC vs the placebo arm, at first it looked favorable, and then it all came together and appeared to have no difference whatsoever.

The challenge was, could there be polymorphisms involved that influenced that outcome? Could there be a reason that the early part of the trial looked like NAC was effective but then disappeared? Given those 2 genes were located very close to each other, we selected 5 polymorphisms that were located in TOLLIP that we knew were functional, and that's what this slide shows you. It shows you polymorphisms, DNA locations that influenced either the promoter region, the exon, which is the actual product level, or the micro-RNA binding site, which also limits production. We knew that these SNPs were involved in susceptibility and survival and function. We took a look at those and we added in the MUC5B promoter SNP because of its proximity and of its high influence in outcomes.

We conducted genotype counts and frequencies using the Chi-square and Fisher's exact test to look at the drug-gene interaction in a multi-variable Cox regression model, applying a Bonferroni correction.

To get enough events, we used a composite endpoint of death, hospitalization, and transplant, or decline in FVC. And then we used an additive model for the TOLLIP polymorphisms, and a dominant model was used for all other SNPs.

In the PANTHER dataset, 341 patients were enrolled, 315 were eligible for the analysis, 154 enrolled in the genetic substudy, giving us 54 patients assigned to the placebo arm and 60 assigned to the NAC arm.
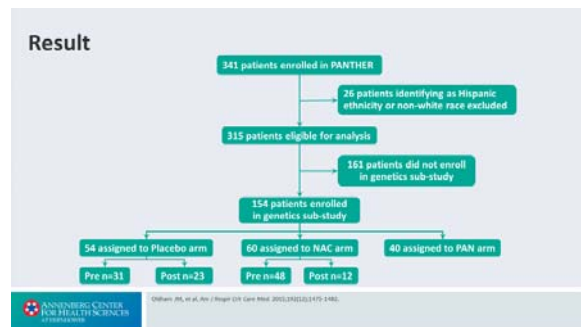
While there were no differences in the pre and post, I am showing you on the demographics what this population looked like, and they were even across the board. Really no differences involved in any of the traits between any of the arms. And at the bottom of the slide we see the genetics of those polymorphisms laid out in those arms with no real differences. And so we know the nongenotype group, again no differences were observed, so if we had powered this for the entire group we would've had a much greater power to determine even more polymorphisms.

As we looked at the drug-gene interaction table we still successfully hit several polymorphisms. Most importantly was RS3750920 in TOLLIP that had a clear interaction with N-acetylcysteine. There were also suggestions, just missing the mark in 2 others. One in TOLLIP and 1 in the MUC5 polymorphism with a *p* value of 0.06 and 0.07 respectively.


With 2 other genes hitting the mark, or just missing a mark, we went on to a replication cohort to confirm our findings, and what we found was that we were able to confirm them in the original 3750920. What's most fascinating is if you take a look at the panel on the left you see that NAC was actually harmful, with a hazard ratio of 3.23, whereas in the panel on the right it was helpful, with a hazard ratio of 0.14. Translating that ratio you were 7-fold less likely to die or hit the composite endpoint with a proper polymorphism, and 3 times more likely to die with the other polymorphism. What does this translate into? The CC polymorphism represents the homozygote major, that's 25% of the populous. The CT is the heterozygote at 50% and the TT is the homozygote minor at 25%. In other words, a quarter of the patients benefited greatly from NAC, whereas a quarter of them were harmed, giving us a flat representation that we saw on the study results.

Results: rs3750920 (TOLLIP) genotype-stratified composite endpoint-free survival between NAC and placebo arms
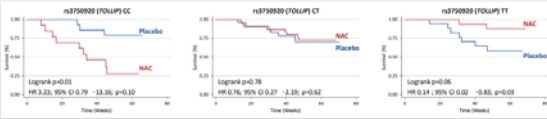
- Harm associated with NAC therapy in those with rs3750920 (*TOLLIP*) CC genotype driven primarily by hospitalizations
- Benefit associated with NAC therapy in those with rs3750920 (*TOLLIP*) TT genotype consistent across all endpoints

When we took a look at the replication cohort, as we pointed out, only the 3750920 held up with very similar hazard ratios of 5 and 0.22.

Results: Replication cohort

On replication, only *TOLLIP* rs3750920 achieved a Bonferroni corrected interaction ($P < 0.01$)

What were our conclusions or takeaways? NAC may be effective in 1 out of 4 patients. This would be the first pharmacogenetic interaction ever demonstrated in IPF. No real clinical traits were noted to be different between the group that was genotyped and not genotyped. And there were certainly no genotype differences by treatment arm or enrollment period.

And that we were able to replicate these findings really become supportive of trying to look at a future trial. These findings really supported ongoing universal genotyping in future NIH trials such as CLEANUP.

We've currently proposed a new N-acetylcysteine-driven trial driven by genotype. The hypothesis is that we should treat only that subgroup of 1 in 4 patients. And that we will do a double-blind, randomized, placebo-controlled trial, 200 subjects, with a TT genotype, over a 2-year duration, where we'll allow pirfenidone and nintedanib in the background and randomize patients to receive the N-acetylcysteine, 600 mg, 3 times a day, for 24 months, to match placebo.

The primary endpoint will be a timed categorical decline in FVC, DLCO, first respiratory, nonelective hospitalization, transplant, or mortality from any cause. The inclusion exclusion criteria, very light. The whole idea here is to really focus on the genotype. Clearly, we would need to screen 4 times as many patients, so somewhere between 800 and 1000 patients to enroll those 200 patients to be randomized with a TT genotype.

Where are some of the areas that precision medicine can help us move? As we discover new targets, using systems and new approaches, we help define molecular characteristics of reprogrammed alveolar epithelial cells. This allows for future big science collaboration of researchers to expedite identification of mechanisms and targets, and allows development of better clinical models that incorporate the effects of aging and relevant genetic information. It also allows us to integrate omics type level data such as I've just shown you from whole genome sequencing and incorporation of gene-environment studies which have yet to be conducted. We need further development and validation of these patient-reported outcomes and biomarkers to help in establishment of an iterative process to incorporate the results in ongoing studies to improve future designs of therapeutic trials so we can execute them in a more rapid fashion.

What can we summarize? I think we've made great inroads on many of the precision models involving genetics, genomics, and other omic platforms. Comorbidities can be viewed as personalized, and precision approaches as well. I think we've started to really bridge the gap to

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move towards pharmacogenetics in a field that desperately needs it. I think that we're able to really start to bridge how we then create study designs that will help foster faster enrollment, shorter timeframes, and more rapid development of precision medicine models.